August 10, 2005

VIA OVERNIGHT MAIL

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852
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CITIZEN PETITION

Insmed, Inc. ("Insmed") submits this Citizen Petition ("Petition") under 21 C.F.R. § 10.30 requesting rejection by the Food and Drug Administration ("FDA" or "the Agency") of the New Drug Application ("NDA") submitted by Tercica, Inc. ("Tercica") under § 505(b)(1) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") for INCRELEX (mecasermin [rDNA origin] injection), recombinant human Insulin-like Growth Factor-I ("rhIGF-I"), for the long-term treatment of growth failure in children with a severe form of primary IGF-I deficiency ("Severe Primary IGFD").

I. ACTION REQUESTED

Insmed requests that FDA immediately deny approval of the NDA for INCRELEX, because Tercica has failed to adequately show the safety of its investigational new drug. Specifically, Insmed believes that Tercica's NDA does not include data that adequately ascertain and document the risk of hypoglycemia and other serious adverse events ("AEs") associated with exogenous rhIGF-I administration in patients with Severe Primary IGFD. Indeed, available safety data show that additional study of the drug may be necessary to demonstrate safety. In addition, Insmed contends that the clinical data reportedly submitted by Tercica in its NDA was obtained from the treatment of subjects with Growth Hormone Insensitivity Syndrome ("GHIS"), for which only approximately 200 have been identified worldwide.[1] Furthermore, this data is

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[1] See Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J. Growth hormone (GH) insensitivity due to primary GH receptor deficiency. **Endocr Rev.** 1994 Jun;15(3):369-390 [enclosed as Attachment 1].

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insufficient to address the intended target population of Severe Primary IGFD, with an estimated prevalence of 12,000 in the U.S. and Western Europe.[2]

II. STATEMENT OF GROUNDS

A. Background

Tercica announced on February 28, 2005 that the company filed an NDA with FDA for INCRELEX that includes the results of a "Phase 3 clinical trial" of rhIGF-I for the treatment of short stature caused by Severe Primary IGFD.[3] The company reported on May 2, 2005 that the Agency filed the application with "priority" review, and assigned an action goal date of August 31, 2005.[4]

On information and belief, Tercica's so-called "Phase 3 clinical trial" results include primarily data derived from a "compassionate use program" for rhIGF-I in GHIS

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2 See Tercica, 10-K Annual Report, 6-7 (Mar. 24, 2005) (available at <http://www.shareholder.com/Common/Edgar/1262175/1193125-05-59908/05-00.pdf>) ("Approximately 380,000 children in the United States are currently referred to pediatric endocrinologists for evaluation of possible short stature. Of these children, we believe that approximately 30,000 in the United States and an equal number in Western Europe, for a total of 60,000 children, have Primary IGFD and may be treated with Increlex. We believe that this represents an approximate $1.0 billion annual market opportunity. . . . We estimate that a total of 12,000 children in the United States and Western Europe have Severe Primary IGFD. We believe that Severe Primary IGFD represents up to an approximate $200 million annual market opportunity in the United states and Western Europe.") [cover enclosed as Attachment 2].

3 See Tercica Press Release, "Tercica Submits New Drug Application for Increlex as a Treatment for Short Stature Caused by Primary IGF-I Deficiency," (Feb. 28, 2005) (available at <http://investor.tercica.com/releases.cfm>). FDA's Office of Orphan Products Development originally designated mecasermin as an orphan drug on December 12, 1995 for the treatment of Growth Hormone Sensitivity Syndrome ("GHIS"). Tercica's NDA seeks approval for Severe Primary IGFD [enclosed as Attachment 3].

4 See Tercica, Press Release, "FDA Accepts Tercica's Increlex New Drug Application With Priority Review for the Treatment of Short Stature" (May 2, 2005) (available at <http://investor.tercica.com/releases.cfm>) [enclosed as Attachment 4].

that was initiated by Genentech, Inc. ("Genentech"), many years ago,[5] plus data to demonstrate the structural and functional comparability between the Genentech-manufactured rhIGF-I and Tercica-manufactured INCRELEX. As explained below, Insmed believes there are legal and public health reasons why FDA cannot approve INCRELEX based on the data submitted in the INCRELEX NDA.

B. Argument

Tercica's rhIGF-I is a recombinant therapeutic protein manufactured by a complex biosynthetic process that is intended for patients with Severe Primary IGFD as a monotherapy. Consequently, the only way for FDA to determine the safety and efficacy of such a product is from full reports of adequate and well-controlled pivotal Phase 3 clinical trials specifically designed to evaluate the product's safety and efficacy profile in the intended patient population, and from manufacturing information. Based on publicly available information concerning the clinical study of INCRELEX, it appears that Tercica has not met its burden of demonstrating the product's safety. As a result, FDA cannot reasonably determine that INCRELEX is safe for the treatment of children with Severe Primary IGFD, and should immediately deny approval of Tercica's NDA.

1. FDA Approval Depends on a Finding that a Drug is "Safe for Use."

To approve a "new drug" under the FDC Act, FDA must determine, based on the applicant's "full reports of investigations," that the drug is "safe for use and [that] such drug is effective in use." FDC Act § 505(b)(1). To determine whether a drug is "effective in use" and "safe for use," FDA evaluates, generally, whether the drug "fulfills, by objective indices, its sponsor's claims of prolonged life, improved physical condition, or reduced pain," and whether "the drug's potential for inflicting death or physical injury is offset by the possibility of therapeutic benefit," respectively.[6] Thus, in FDA's risk-benefit analysis for purposes of acting on a marketing application for a new drug, the two concepts of "safety" and "efficacy" are inseparable, but must be independently shown.

In order to independently show the safety of an investigational new drug for a proposed use, a sponsor must accurately and consistently document and analyze the

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5 See Ratner ML. Tercica: growing small. Start-Up: Windhover's Review of Emerging Medical Ventures. 2004 Dec;9(11):13-18 [enclosed as Attachment 5].

6 United States v. Rutherford, 442 U.S. 544, 555-56 (1979).

incidence and severity of AEs affecting the product's safety profile.[7] If FDA finds that a sponsor's investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof [, or] the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions [, or if there] is insufficient information to determine whether such drug is safe for use under such conditions . . . [FDA] shall issue an order refusing to approve the application."[8]

The regulations implementing FDC Act § 505(d) with respect to safety issues are found at 21 C.F.R. § 314.125(b), and essentially parallel the statutory language:

> FDA may refuse to approve an application for any of the following reasons:
>
> (1) ....
>
> (2) The investigations required under section 505(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.
>
> (3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.
>
> (4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.[9]

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7 See generally 21 C.F.R. § 314.50(d)(5).

8 FDC Act § 505(d)(1), (2), (4).

9 21 C.F.R. § 314.125(b).

2. *Hypoglycemia is a Well-Established, Dose-Limiting AE Associated with Exogenous, Free rhIGF-I Administration.*

Hypoglycemia (low blood glucose) is a well-established property associated with exogenous rhIGF-I administration.[10] Hypoglycemia is a serious condition characterized by a reduction in plasma glucose concentration to a level (generally defined as a serum glucose level below 60 mg/dL) that may induce symptoms of low blood sugar. In extreme cases, severe hypoglycemia (generally defined as a serum glucose level below 30 mg/dL) can result in altered mental status, seizure, coma, cardiac dysrhythmia, and death.

IGF-I is "insulin-like" in its effects on lowering blood glucose levels and is found in human circulation predominantly in association with the GH-dependent IGFBP-3. This binary complex further combines with a third protein typically found in excess in the circulation, the GH-dependent acid-labile subunit ("ALS"), to form a ternary complex (i.e., IGF-I/IGFBP-3/ALS), which represents the natural physiologic reservoir of IGF-I. In the bound state, IGF-I is biologically inactive.

Unlike free IGF-I, which can readily cross the vascular endothelium, the ternary complex, due to its size (140-150kD), is restricted from leaving the vasculature and from binding the IGF receptors found in tissues throughout the body. The binding proteins modulate IGF-I bioactivity by delivering it to the tissues in a regulated manner, thus facilitating the growth-promoting actions while buffering the acute insulin-like effects that can result in hypoglycemia.[11] The binding proteins also effectively prolong the half-life of IGF-I from ~15 minutes for the free protein to >12 hours for the ternary complex. Because high doses of free rhIGF-I are limited by the occurrence of severe hypoglycemia and the rapid clearance of free IGF-I from the circulation, rhIGF-I has been administered as twice-daily, split-dose, injections in most clinical investigations, including clinical investigations of the Genentech and the Tercica products.

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10 See e.g., Firth SM, McDougall F, McLachlan AJ, Baxter RC. Impaired blockade of insulin-like growth factor I (IGF-I)-induced hypoglycemia by IGF binding protein-3 analog with reduced ternary complex-forming ability. **Endocrinology** 2002 May;143(5):1669-76 [enclosed as Attachment 6]; Guler HP, Zapf J, Froesch ER. Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults. **N Engl J Med.** 1987 Jul 16;317(3):137-40 [enclosed as Attachment 7].

11 See Firth et al., supra, note 9.

In the circulation, most IGFBP-3 is occupied with either IGF-I or IGF-II in an equimolar balance, and therefore, there is no excess reservoir of free IGFBP-3. Thus, circulating IGFBP-3 is generally not available to bind the majority of rhIGF-I administered in the free form.

The global experience with free rhIGF-I therapy in a variety of indications has shown hypoglycemia to be the primary dose-limiting factor and the major reason why the drug is administered in lower doses twice-daily rather than as a higher dose once-daily. The risk of hypoglycemia appears to be related to the amount of free rhIGF-I reaching target tissues, where it exerts its insulin-like actions at the IGF-I receptor, insulin receptor, or a combination of both. By forming binary and ternary complexes with IGFBP-3 and ALS, IGF-I is normally prevented from circulating in high concentrations in its biologically-active free state.

3. FDA Must Deny Approval of INCRELEX, Because Tercica's Investigations do not Adequately Address the Risk of Hypoglycemia and other AEs Associated With rhIGF-1 in the Treatment of Severe Primary IGFD.

On information and belief, Tercica's "full reports of investigations" of the safety and efficacy of INCRELEX are largely based on a retrospective analysis of data collected from a "compassionate use program" with rhIGF-I in GHIS sponsored by Genentech several years ago.[12] Typically, "compassionate use programs" are not designed to provide rigorous evidence of the safety of a drug, and therefore, such studies tend to underreport the incidence and severity of AEs.

In controlled clinical trials designed to determine the safety and efficacy of an investigational drug, a detailed protocol, data collection forms and investigator training sessions are used to ensure the consistent conduct of the trial and collection of information for all participating patients. In "compassionate use programs," treating physicians are not typically required to attend training sessions or investigator meetings in which they would learn the type and presentation of AEs associated with the use of the investigational drug. In most "compassionate use programs," treating physicians are only given very general guidelines and often report information in the form of physician notes rather than on detailed data collection forms. In addition, treating physicians participating in "compassionate use programs" are typically not monitored by the sponsor or their representatives nearly as often as they are in controlled clinical trials (and sometimes not at all).

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12 See Ratner, supra, note 5.

For these reasons, it is likely that AEs including hypoglycemia may have been missed or overlooked and therefore the true risk of hypoglycemia and other AEs in subjects administered exogenous rhIGF-I in Genentech's "compassionate use program" is not fully known. Moreover, in prospective clinical trials conducted using the identical rhIGF-I molecule as in the Genentech/Tercica program, but manufactured by different companies, it has been shown that there is sufficient risk of various AEs to require careful, prospective monitoring and validation of the data. Based on this information, FDA cannot legally approve INCRELEX without first obtaining further data from adequate and well controlled clinical studies that are rigorously conducted to gather all AEs and closely monitored to better assure the fidelity and accuracy of the AEs reported, and which further data demonstrate the safety of the drug product in the target population.

a. Tercica's Investigations did not Likely Include Adequate Investigator Training, Monitoring and Data Collection by All Methods Reasonably Applicable to Show Whether or Not INCRELEX is Safe for Use in Patients with Severe Primary IGFD.

It is unlikely that the investigations on which Tercica relies for approval included adequate tests to show whether or not INCRELEX increased the incidence of all serious AEs associated with hypoglycemia.[13] Without data from adequate studies documenting the incidence and severity of hypoglycemia and related events associated with INCRELEX, FDA cannot reach a conclusion as to the safety of the drug, and should

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[13] In fact, in December 2003, FDA issued an approvable letter to Amylin Pharmaceuticals, Inc. for the company's NDA for SYMLIN (pramlintide acetate) Injection, 5 mL vials (NDA #21-332) after FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted that Amylin's data and study designs were inadequate to show the drug's safety profile. Specifically, advisory committee members were concerned with the increased risk of hypoglycemia, and found Amylin's hypoglycemia safety data to be inadequate to address their concern. FDA requested "additional clinical data to identify a patient population and method of use for Symlin where there is no increased risk of significant hypoglycemia or where there is an added benefit that clearly counterbalances any potential for increases in episodes of hypoglycemia." F-D-C Reports, Inc., "The Pink Sheet" 65(51):20 (Dec. 22, 2003). Symlin "Approvable" Letter Will Be Addressed By Ongoing Trials, Amylin Says [enclosed as Attachment 8].

refuse to approve the NDA. Approval of INCRELEX without adequate tests to show the safety of the drug could jeopardize the public health.

Accurate documentation and analysis of the incidence and severity of hypoglycemia and other AEs in adequate and well-controlled investigations depends on frequent monitoring of the investigators and consistent collection of data. Typically, "compassionate use programs" are not designed to provide rigorous evidence of the safety profile of a drug, and therefore, such studies tend to underreport the incidence and severity of AEs. Tercica's safety data for INCRELEX are largely based on the results from 65 GHIS subjects administered the drug in a multi-center, open-label "compassionate use program" reported by Louis Underwood, M.D. and Steven Chernausek, M.D.[14,15] This retrospective collection of clinical data, which here apparently is represented as a Phase 3 study, likely underreported the incidence and severity of hypoglycemia and other AEs and is likely inadequate to show that INCRELEX is safe for use in the proposed target population of Severe Primary IGFD.

Disposition of Subjects. In a poster presented at the 2004 Endocrine Society Annual Meeting, Tercica reported on 65 subjects treated with rhIGF-I for up to 10.5 years (median = 3.5 years).[16] Based on this report, at least 32 (one-half of 65) subjects should have been active after 3 years of the study. However, in a related poster presented at the same Endocrine Society meeting, Tercica reported efficacy data for only 24 subjects at 3 years.[17] The lack of efficacy data for several enrolled subjects implies incomplete subject follow-up and/or a greater number of early withdrawals than that reported by Tercica.

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14 See Underwood L, Chernausek SD, Kuntze J, Frane J, Bright GM. Efficacy of long-term treatment with recombinant human IGF-I (rhIGF-I) of children with GH insensitivity [abstract no. P3-451]. Presented at: **The Endocrine Society's 86th Annual Meeting**, New Orleans, June 2004 (hereinafter "Tercica Efficacy Poster") [enclosed as Attachment 9].

15 See Chernausek SD, Underwood L, Kuntze J, Frane J, Bright GM. Safety of recombinant human IGF-1 in the treatment of children with IGF-1 deficiency due to GH insensitivity: 231 treatment-years of experience [poster]. Presented at: **The Endocrine Society's 86th Annual Meeting**, New Orleans, June 2004 (hereinafter "Tercica Safety Poster") [enclosed as Attachment 10].

16 See id.

17 See Tercica Efficacy Poster, supra note 14.

Tercica reports that in subjects treated up to 10.5 years with rhIGF-I, none withdrew from treatment due to AEs.[18] This has not been the case in other carefully monitored studies of rhIGF-I in GHIS. Of the 65 subjects reported in the safety poster, reasons for discontinuation were given for 11 subjects (3 completed therapy, 4 noncompliance, 4 lost to follow-up), whereas only 12/65 subjects had efficacy data reported at the final timepoint in the companion poster. It is unclear why the disposition for the remaining 42 subjects was not provided.

The Quality of Tercica's Clinical Data is Highly Suspect. FDA's "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" emphasizes the importance that, with respect to the quality of evidence necessary to support FDA approval, the adequacy of the scientific evidence must be assured. This includes complete records and documentation of study conduct and the "ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence."[19] A close review of Tercica's published clinical data, and particularly Tercica's published safety data, suggests they may be of poor quality.

The number (%) of subjects reporting frequent and related AEs in all 65 subjects reported in Tercica's Safety Poster was compared with published data on a subset of 8 of these patients monitored at a single site.[20] The comparison suggests that certain AEs may have been under-reported by some of the treating physicians.

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18 See Tercica Safety Poster, supra note 15.

19 See FDA, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (May 1998), at 16.

20 See Backeljauw PF, Underwood LE; GHIS Collaborative Group. Prolonged treatment with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome- a clinical research center study. **J Clin Endocrinol Metab.** 1996 Apr; 81(9):3312-17 [enclosed as Attachment 11]; Underwood LE, Backeljauw P, Duncan V, GHIS Collaborative Group. Effects of insulin-like growth factor I treatment on statural growth, body composition and phenotype of children with growth hormone insensitivity syndrome. **Acta Paediatr Suppl.** 1999; 428:182-184 [enclosed as Attachment 12]; Backeljauw PF, Underwood LE; GHIS Collaborative Group. Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study. **J Clin Endocrinol Metab.** 2001;86(4):1504-1510 [enclosed as Attachment 13].

The comparison (Table 1) shows that a significantly greater proportion of subjects in the 8-subject subset reported certain AEs than would be expected (25% vs. 5% for total subject cohort). The discrepancies in safety reporting suggest either that the Investigator at the site where the 8 subjects were evaluated paid closer attention to his patients or that the conduct of the study at the 8-subject site was monitored more closely than other sites, or both. At a minimum, the data suggest that the conduct of the study across study sites was inconsistent.

Table 1. Tercica Data; Intra-Study Comparison of Certain AEs

Adverse Event	Chernausek et al. 2004 (n=65) # of Subjects (%)	Backeljauw et al., 1996, 2001 (n=8) # of Subjects (%)
Tonsillectomy /adenoidectomy	3 (5%)	2 (25%)
Intracranial hypertension	3 (5%)	2 (25%)

Finally, in a poster presented by Tercica at the 2005 Endocrine Society Annual Meeting concerning neutralizing antibodies,[21] the company reported on only 22 (31%) of 71 pediatric subjects studied. The lack of data on 69% of study subjects suggests that that immunogenicity was not monitored by all investigators throughout the study or that the immunogenicity screening was not prospectively planned. Because antibodies develop in response to ongoing treatment and the presence and magnitude of the antibody response changes over time, the lack of consistent sampling and testing during the course of treatment may have missed the antibody peak, leading to under-reporting of true positive antibody incidence and peak titer. The data provided do not demonstrate that evaluation of the time-course of the antibody response was rigorously evaluated.

b. Even if FDA Determines that Tercica's Tests are Adequate, Data on free rhIGF-I Show either that INCRELEX is Unsafe for Use, or they do Not Show that INCRELEX is Safe for Use in Patients with Severe Primary IGFD.

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21 See Clark R, Frane J. and Bright, G. Long-term Therapy with rhIGF-1: No evidence of Neutralizing Antibodies [poster P1-493]. Presented at: **The Endocrine Society's 87th Annual Meeting**, San Diego, June 2005 [enclosed as Attachment 14].

Clinical Studies of rhIGF-I Show an Unacceptable Increased Risk of Hypoglycemia and Other AEs. Numerous AEs reported in patients receiving exogenous, free rhIGF-I treatment raise important safety concerns that may require additional clinical studies with INCRELEX. For example, in a poster presentation of 65 subjects with GHIS treated up to 10.5 years in the Genentech/Tercica program, AEs included hypoglycemia (26 subjects), tonisillectomy/adenoidectomy (3 subjects), and intracranial hypertension (3 subjects).[22] However, Tercica's clinical information is unlikely to be comprehensive with respect to safety reporting, based on a review of the published literature of formal prospective clinical trials of rhIGF-I in GHIS.

In a report of 8 of the subjects with GHIS treated with rhIGF-I, included as part of the Genentech "compassionate use program," AEs included intracranial hypertension (2 subjects), tonsillectomy/adenoidectomy (2 subjects), and hypoglycemic seizure (1 subject).[23] In that study, hypokalemia was noted on several occasions 1-3 hours post injection, however, electrocardiogram recordings were not obtained to further assess this event, which is likely related to the acute rise in free rhIGF-I. Increased urinary calcium excretion was also noted in that study, which may explain the occurrences of nephrolithiasis and renal colic in other rhIGF-I studies.

In a study of 33 subjects with GHIS treated for up to 2 years with rhIGF-I identical to Tercica's rhIGF-I, AEs included headache (21 events in 13 subjects), severe hypoglycemia (13 events in 4 subjects), tonsillectomy/adenoidectomy (3 subjects), renal colic (2 subjects), facial nerve paralysis (1 subject), papilledema (1 subject) and dizziness/ hypokalemia (1 subject).[24]

In the 6-month blinded phase of a placebo-controlled study of 17 GHIS subjects in Ecuador treated with rhIGF-I identical to Tercica's rhIGF-I,, symptomatic hypoglycemia occurred in 3 rhIGF-I subjects (4 occasions) and none of the 9 placebo subjects. In addition to others, papilledema, headache, blurred vision were also reported. A description of this study is in Guevara-Aguirre, 1995.[25] In another Ecuadorian study of 8

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22 See Tercica Safety Poster, supra note 15.

23 See Backeljauw et al. 1996 and 2001, supra note 20.

24 See Ranke MB, Savage MO, Chatelain PG, Preece MA, Rosenfeld RG, Blum WF, et al. Insulin-like growth factor I improves height in growth hormone insensitivity: two years' results. **Horm Res**. 1995;44(6):253-264 [enclosed as Attachment 15].

25 See Guevara-Aguirre J., et al. A randomized, double blind, placebo-controlled trial on safety and efficacy of recombinant human insulin-like growth factor-I in children with growth hormone receptor deficiency. **J Clin Endocrinol Metab.**

GHIS subjects treated with rhIGF-I identical to Tercica's rhIGF-I, AEs included, among others, symptomatic hypoglycemia, facial nerve palsy, headache, nausea and vomiting. This study is described in Guevara-Aguirre, 1997.[26]

In a letter to the editor of the New England Journal of Medicine authored by members of the FDA, it was reported that FDA had received reports that intracranial hypertension developed in three patients treated with rhIGF-I within 16 weeks after treatment was begun.[27] All patients presented with papilledema, which disappeared after the treatment was stopped. In addition, in another letter authored by members of the FDA to the editor of the Annals of Internal Medicine, it was reported that FDA had received reports of syncopal reactions in 11 patients treated with rhIGF-I either intravenously or subcutaneously.[28] The report stated: "It seems attractive to speculate that when the capacities of IGF-binding proteins are exceeded, the high levels of free IGF-I could result in these short-term adverse events."

Increased Risk of Hypoglycemia with Multiple Injections per Day. Each injection of rhIGF-I is expected to be followed by a fall in serum glucose, and therefore, carries a certain risk of being symptomatic and possibly leading to a serious AE, such as coma and/or seizure. Patients treated with injections of rhIGF-I in the morning and again in the evening have a risk each time of developing hypoglycemia, depending on the predisposition of the patient and his/her concurrent hormonal and nutritional status.

Indeed, the complication of hypoglycemic events with more frequent dosing of a glucose-lowering medication was demonstrated by the Diabetes Control and Complications Trial ("DCCT").[29] In that study of 1441 patients with Type 1 diabetes

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1995 Apr;80(4):1393-8 [enclosed as Attachment 16]

[26] See Guevara-Aguirre J, Rosenbloom AL, Vasconez O, Martinez V, Gargosky SE, Allen L, et al. Two-year treatment of growth hormone (GH) receptor deficiency with recombinant insulin-like growth factor I in 22 children: comparison of two dosage levels and to GH-treated GH deficiency. **J Clin Endocrinol Metab.** 1997 Feb;82(2):629-633 [enclosed as Attachment 17].

[27] See Malozowski S, Tanner LA, Wysowski D, Fleming GA. Growth hormone, insulin-like growth factor I, and benign intracranial hypertension [letter]. **N Engl J Med.** 1993;329(9):665-666 [enclosed as Attachment 18].

[28] See Malozowski S, Stadel B. Risks and benefits of insulin-like growth factor [letter]. **Ann Int Med.** 1994;121(7):549-550 [enclosed as Attachment 19].

[29] See The DCCT Research Group. The effect of intensive treatment of diabetes on

mellitus, subjects were randomized to receive insulin either by conventional 1-2 injections/day or by more intensive 3 or more injections/day or pump. The chief AE associated with intensive therapy was a 3-fold increase in severe hypoglycemia. There were 3,788 episodes of severe hypoglycemia (requiring assistance), of which 1,027 episodes were associated with coma and/or seizure.[30]

A total of 65% percent of patients in the intensive group, versus 35% of patients in the conventional group, had at least one episode of severe hypoglycemia by study end. However, total daily insulin doses were similar in the two groups.[31] Whereas HbA1c levels were lower in the intensive treatment group, intensive treatment was still associated with a significantly increased risk of hypoglycemia even after adjustment for differences in HbA1c levels. This indicates that the increased hypoglycemia risk with intensive treatment is not completely explained by differences in HbA1c values and may be related to the frequency of injection.

The analogy of insulin therapy in diabetics and IGF-I therapy in GHIS or Severe Primary IGFD is an appropriate one. Insulin and IGF-I have similar glucose-lowering properties, owing to their ability to cross-react at their respective receptors. IGF-I has a further insulin sensitizing effect. The risk of hypoglycemia in diabetics is thought to be largely due to a lack of counter-regulatory hormones, which is also the case in GHIS or Severe Primary IGFD patients who may lack the critical activity of GH in their glucose metabolism. The association of missed meals and excessive or unplanned exercise with development of hypoglycemia in diabetics treated with intensive insulin is also similar to what has been observed with rhIGF-I in GHIS patients. It is Insmed's belief that twice daily administration of rhIGF-I, which Insmed understands to be the proposed dosing regimen for INCRELEX, will have approximately twice the risk of hypoglycemic episodes.

The risk of hypoglycemia with twice-daily administration of free rhIGF-I is a clear safety signal that may carry unacceptable risks. Measures such as careful timing of meals, frequent blood glucose monitoring, and withholding dose for low glucose levels

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the development and progression of long-term complications in insulin-dependent diabetes mellitus. **N Engl J Med.** 1993;329:977-86 [enclosed as Attachment 20].

30 See The DCCT Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. **Diabetes** 1997;46:271-86 [enclosed as Attachment 21].

31 See Genuth S. Exogenous insulin administration and cardiovascular risk in non-insulin-dependent and insulin-dependent diabetes mellitus. Ann Intern Med. 1996;124:104-9 [enclosed as Attachment 22].

have been employed in most rhIGF-I studies in GHIS, with glucagon therapy made available in the event of severe hypoglycemia. Whereas these measures may have successfully reduced the incidence of hypoglycemia in the controlled clinical trial setting, this would not be feasible or expected in the real-world setting with this treatment, in which unrestricted use may have dire consequences.

Clinical experience reported using physically identical rhIGF-I drug products shows a significant risk of hypoglycemia at effective doses. At a minimum, Tercica's data do not conclusively demonstrate that INCRELEX is safe for use in patients with GHIS or Severe Primary IGFD with respect to the risk of hypoglycemia. Additional safety data in the target population, obtained in a prospective manner with thorough monitoring of investigations are needed. Therefore, to adequately show the product's safety, FDA should refuse to approve the NDA and require Tercica to generate additional safety data from an adequate and prospective study of the target population.

c. There is Insufficient Information About INCRELEX for FDA to Determine Whether the Drug is Safe for Use in Patients with Severe Primary IGFD.

The Genentech "compassionate use program" was in subjects with GHIS, all of whom had either GH receptor defects or GH gene deletion (except for 2 subjects with "unknown etiology"). This population does not correspond with Tercica's definition of Severe Primary IGFD. Tercica has publicly stated that GHIS and Severe Primary IGFD, while related, are not the same condition. Tercica recently stated in a document filed with the Securities and Exchange Commission ("SEC") that:

> Our original plan was to obtain rhIGF-I orphan drug designation for the treatment of growth hormone insensitivity syndrome, or GHIS. The Phase III clinical trial results we obtained from Genentech were for GHIS. Everywhere in this document where we discuss existing Phase III clinical trial results such results were from patients identified at the time as having GHIS. Since we now believe that Severe Pediatric IGFD, which is [sic] we believe substantially equivalent to GHIS, more accurately describes the patient population which we intend to treat with rhIGF-I, we plan to amend our current [orphan drug] designation to cover Pediatric IGFD, but may as a result of comments from the FDA continue with a GHIS designation, which may be a smaller patient population.[32]

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[32] See Tercica, S-1 Registration Statement, at 8 (Sept. 12, 2003) (available at <http://www.sec.gov/Archives/edgar/data/1262175/000119312503048598/ds1.htm>) [enclosed as Attachment 23].

Clearly, Tercica believes that GHIS and Severe Primary IGFD are different conditions, with different prevalences. GHIS as defined in most clinical trials involving IGF-I treatment is an extremely rare condition with only approximately 200 cases identified worldwide.[33] According to Tercica, however, Severe Primary IGFD, on the other hand, affects approximately 12,000 children in the U.S. and Western Europe.[34]

Despite Tercica's belief that GHIS and Severe Primary IGFD are different conditions with different prevalences, the company, apparently believes that the Genentech/Tercica "compassionate use program" for rhIGF-I in GHIS subjects is sufficient to show the safety of INCRELEX in patients with Severe Primary IGFD. However, it seems implausible that FDA would find limited safety data from a "compassionate use program" in a very small population to be sufficient to determine that INCRELEX is safe for use in patients with a condition which is significantly more prevalent. It appears that Tercica's safety data are insufficient for FDA to determine that INCRELEX is safe for use in patients with classically-defined GHIS, and therefore, such safety data has to be even more inadequate to assure the safety of its use in patients in the much broader target population of Severe Primary IGFD.

C. Conclusion

In order for FDA to approve Tercica's NDA for rhIGF-I, the Agency must determine, under the FDC Act and its regulations, that the drug is safe for its proposed use. Based on publicly available information concerning Tercica's "full reports of investigations" for INCRELEX, it appears that Tercica has not met its burden of showing safety. Specifically, Insmed believes that Tercica's investigations did not include adequate investigator training, monitoring and data collection methods needed to show the true risk of hypoglycemia and other AEs in children with GHIS or Severe Primary IGFD. Moreover, available data show that there are important safety concerns associated with exogenous, free rhIGF-I administration that may require additional study. Finally, there appears to be insufficient information about INCRELEX for FDA to determine whether the drug is safe for use in Severe Primary IGFD patients.

Because FDA cannot reasonably determine, based on the data we believe Tercica has submitted in the company's NDA, that INCRELEX is safe for the treatment of children with GHIS or Severe Primary IGFD, the Agency should immediately deny approval of Tercica's marketing application.

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[33] See Rosenfeld et al. 1994, supra, note 1.

[34] See Tercica, 10-K Annual Report, 6-7 (Mar. 24, 2005), supra, note 2.

III. ENVIRONMENTAL IMPACT

The actions requested in this Petition are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22. Additionally, the actions requested in this Petition are exempt from requirement of an environmental assessment pursuant to 21 C.F.R. §§ 25.30, 25.31.

IV. ECONOMIC IMPACT

Information on the economic impact of this proposal can be provided if requested.

V. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes information and views on which the Petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the Petition.

Respectfully Submitted,

Geoffrey Allan, Ph.D.
President & Chief Executive Officer